Pheochromocytoma in dogs: a diagnostic challenge

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Pheochromocytoma: how to diagnose it?

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Pheochromocytomas are catecholamine-producing neuroendocrine tumors arising from chromaffin cells of the adrenal medulla. Pheochromocytomas are potentially malignant and local invasion into the adjacent vessels and other tissues is seen in more than 50% of dogs, sites of metastasis are regional lymph nodes, spleen, liver, kidney, pancreas, lung, heart, bone and CNS. The tumors are usually slow growing. Size is extremely variable and ranges between a few millimeters and more than 10 cm in diameter.

Most tumors are unilateral, occasionally both adrenal glands are affected. They may coexist with cortisol-producing adrenocortical tumors, ACTH-producing pituitary tumors or other endocrine tumors.

Clinical signs are usually the result of catecholamine excess and/or rarely from the space-occupying or invasive nature of the tumor. Catecholamines bind to α- and β-adrenergic receptors and induce “fright, fight and flight” reactions. Important effects are: increase of heart rate and contractility, increase of blood pressure and respiration rate, relaxation of gastrointestinal tract and urinary bladder, increase of blood glucose and free fatty acids and increased alertness. In healthy dogs the content of the adrenal medulla is approximately 30% norepinephrine and 70% epinephrine. In dogs with pheochromocytoma, the proportion of the hormones may be different from healthy dogs and norepinephrine may be the predominant secretory product. Hormone secretion may be constant or sporadic and is highly unpredictable. The disease may occur at any age, however, it is most commonly seen in older dogs. There are no apparent sex and breed predispositions. The clinical presentation is highly variable. Signs may be apparent several times per day or may only reoccur after days, weeks or months. Severity of the disease ranges from dramatic and life-threatening to very mild. Some pheochromocytomas are hormonally silent.

Clinical signs may be categorized as:

1. non-specific: anorexia, weight loss, lethargy
2. related to the cardio-respiratory system and/or hypertension: tachypnoe, panting, tachycardia, arrhythmias, collapse, pale mucous membranes, nasal-, gingival-, ocular hemorrhage, acute blindness due to retina detachment

3. related to the neuromuscular system: weakness, anxiety, pacing, muscle tremor, seizures
4. miscellaneous: polyuria/polydipsia, vomiting, diarrhoe, painful abdomen.

The most common signs are weakness and episodic collapse. Large tumors may cause abdominal distension, ascites and hind-limb edema. Intra-abdominal or retroperitoneal hemorrhage due to tumor rupture is also possible.

Hypertension is one of the hallmarks of the disease. However, hypertension is not pathognomonic for pheochromocytoma and is also frequently found in hyperadrenocorticism, which is one of the most important differential diagnosis.

Due to the episodic secretion of catecholamines, hypertension is only present in approximately 50% of dogs by the time of examination. Typically, systolic measurements are between 200 and 240 mm Hg, the maximum systolic blood pressure reported so far was 325 mm Hg.

Often pheochromocytoma is only considered after an adrenal mass has been detected by ultrasonography. No pattern of echogenicity or architecture is specific for pheochromocytomas, other adrenal masses e.g. cortisol-producing tumors may look alike. CT and MRI are more sensitive than ultrasonography to identify adrenal masses and to characterize the extent of local invasion, however, they also do not allow a discrimination between pheochromocytoma and other adrenal masses.

In humans, diagnosis of pheochromocytoma is mainly based on biochemical detection of excessive amounts of catecholamines (epinephrine, norepinephrine) and their metabolites (metanephrine, normetanephrine) in 24-h urine or in plasma. Although the question which test (urine or plasma) is best, is still somewhat controversial, plasma metanephrines tended to be recommended increasingly as test of choice. In dogs, evaluation of those biomarkers for the diagnosis of pheochromocytoma has started only a few years ago. Since 24-hours urine sampling is impracticable under clinical conditions, measurements of urinary fractionated catecholamines and metanephrines was established in spot urine samples by expressing their concentrations as ratio to the urinary creatinine concentration. Urinary normetanephrine to creatinine ratio was shown to be the parameter, which differentiated dogs with pheochromocytoma best from healthy dogs and dogs with hypercortisolism. We are currently using a cut-off value of urinary normetanephrine:creatinine ratio of 4 times of normal as being diagnostic for pheochromocytoma. However, lower values do not exclude the disease and repetitive testing may therefore be required. Sample collection and urine processing are subject to certain conditions, such as acidification, light protection, cooled or frozen storage. Close collaboration with the laboratory is therefore necessary.

We recently compared the diagnostic performance of urinary and plasma catecholamines and metanephrines by evaluating healthy dogs and dogs with pheochromocytoma, hypercortisolism or non-adrenal disease. Discrimination of dogs with pheochromocytoma was superior with urinary and plasma normetanephrine compared to urinary and plasma metanephrine. The differences between the urinary and the plasma tests were, however, small. In conclusion, measurement of normetanephrine is the preferred biochemical test for pheochromocytoma. As differences between the urine and plasma test are minor, decision between both tests should be made based on available technical facilities and dog-specific reference ranges.

Adrenalectomy is the treatment of choice and should be performed as soon as possible. It has been shown that perioperative mortality decreases if dogs are pretreated with an α-adrenergic blocker (phenoxybenzamine) for at least 1 - 2 weeks before surgery. In dogs surviving the perioperative period, survival for several years is possible.

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